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(54) INGESTIBLE COATING COMPOSITIONS

(71) We, SANKYO COMPANY LIMITED, of 1-6, 3-chome, Nihonbashi Honcho, Chuo-ku, Tokyo, Japan, a Japanese company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:-

The present invention relates to ingestible coating compositions for use in coating solid pharmaceutical, food and other ingestible preparations, to methods of using the coating compositions, to solid ingestible preparations when given a protective film using the coating compositions, and to solid products for use in the preparation of the coating compositions.

Solid pharmaceutical preparations such as tablets, pills or granules are usually given a protective film in order to prevent degeneration or decomposition of the active ingredient due to the absorption of water or some other cause occuring either during the process of manufacture or during storage until administration of the preparation. The protective film is normally formed using one or more high molecular weight compounds as a coating material. Typical high molecular weight compounds employed for this purpose include shellac, cellulose acetate phthalate (CAP), 2-methyl-5-vinylpyridine-methyl acrylate-methacrylic acid copolymer (MPM), ethylcellulose (EC), and polyvinyl acetal diethylaminoacetate (AEA).

The coating of the high molecular weight compound is usually applied by spray-coating a solution of the compound in an organic solvent with high volatility. In this case, the organic solvent evaporates into the atmosphere along with drying air to become a potential source of atmospheric pollution. It is therefore necessary to wash the air with water to trap the organic solvent. Moreover, in order to maintain a good working environment, it is necessary to employ air-conditioning equipment. The expenditure necessary can be considerable, particularly when one takes into account the cost of the organic solvent and the need for any electrical appliances to be of the anti-explosion type.

Water appears to be a better choice for a coating solvent, but it has not met with acceptance for various reasons. Firstly, there are no suitable water-soluble high molecular weight compounds which can give a protective film which is adequately moisture proof. Secondly, moisture will ordinarily penetrate into the preparation during spraying when an aqueous coating solution is employed.

Liquid coating compositions are already known which are based on water-soluble film-forming compounds which compounds in themselves have poor moisture resistance. The compounds, such as hydroxypropyl cellulose (HPC), hydroxypropyl methyl-cellulose (HPMC), or an organic acid salt of AEA, are blended with stearic acid or the like additive to impart moisture resistance. However, this known composition has the disadvantage that an organic solvent is necessary for dissolving the stearic acid or other additive.

Protective films are frequently used to mask the characteristic properties of active ingredients in an orally administered solid pharmaceutical preparation. Thus one of the important criteria for selection of a protective film is the ability to mask a pungent taste and/or an unpleasant smell for the time that the preparation is in the mouth. This masking

action of the coating film has to be compatible with the ability to release rapidly the contents of the preparation once it has been swallowed. It is most important that the bioavailability of the active ingredient is now lowered. The masking and release characteristics of protective films can be estimated in a dissolution test on the preparation. Any delay in dissolution, i.e. temporary prevention of the release of the active ingredient, and subsequent rapid release of the active ingredient can be observed in these tests. It is usually appropriate that the delay in dissolution is 1 to 5 minutes, and it is desirable to be able to regulate this time freely by selecting the coating material and the conditions employed during the coating process.

In accordance with the present invention there is provided an ingestible coating composition which comprises a non-toxic dispersion of particles dispersed in an aqueous solution of a film-forming polymer. The particles comprise one or more of a metal salt of a fatty acid which acid has a melting point of 40-90°C, a fatty acid having a melting point of 40-90°C, or a wax having a melting point of 40-90°C. The dispersion further contains a non-toxic non-ionic surface active agent with an HLB of less than 9 and/or a silicone oil dissolved in the aqueous solution.

By the use of such compositions it is possible to obtain a protective film which has a good lustre and a smooth taste and which is moisture proof. Moreover, it is readily possible to make a solid preparation with a protective film which has a good masking effect to prevent any active ingredients in the preparation from being released in the mouth before swallowing, and yet which has a determinable delay in dissolution to ensure rapid release of the active ingredients after swallowing.

The coating compositions can be coated onto solid ingestible preparations using conventional techniques. For example, the compositions can be sprayed while causing or allowing water to evaporate from the coating to give a protective film. The coated preparations can be given a further coating layer such as of sugar or gelatin, although the coated preparation in itself usually possesses a glossy, smooth surface which is acceptable for commercial purposes.

The delay in dissolution can be easily and freely regulated by varying the kinds and mixing ratios of the metal salt of the fatty acid, the fatty acid, the wax, the surface active agent and/or the silicone oil, as well as by varying the amount to be coated per unit surface area of the preparation. In this way moisture proof films can be obtained which have the required dissolution characteristics for masking and releasing active ingredients with a bitter taste.

The film-forming polymer employed in compositions embodying the present invention can be one which is soluble in water itself, such as HPC or HPMC, but it can also be a compound which is soluble in other aqueous media. Examples of the latter polymers include salts of AEA obtained by dissolving AEA in an aqueous acid, or a salt of CAP, shellac, or hydroxypropyl methylcellulose phthalate (HPMCP) obtained by dissolving the respective polymer in an aqueous alkali. By way of illustration the salts can be an organic acid salt of AEA, preferably a salt of a dibasic acid; sodium cellulose acetate phthalate or sodium hydroxypropyl methylcellulose phthalate. Other representative examples of water-soluble, film-forming polymers include methylcellulose, hydroxyethylcellulose, sodium carboxymethylcellulose, polyvinyl alcohol, polyvinylpyrrolidone, sodium alginate, and salts of acrylate polymers such as a sodium salt of MPM. The salts of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate or of acrylate polymers will usually be the alkali metal or ammonium salts. When selecting the polymer to be used it is necessary to bear in mind certain characteristics of the various possibilities. For example, HPC is less effective in forming coating films as compared with most of the other compounds. Of the organic acid salts of AEA, the fumarate is to be preferred in view of its low toxicity, acceptable taste and good solubility. When using sodium alginate, it is preferable to employ an alginate prepared by partial hydrolysis and having a lowered viscosity and higher solubility. Sodium cellulose acetate phthalate tends to release acetic acid upon prolonged storage and as such is not preferred.

The fatty acids employed are higher fatty acids and have a melting point of 40-90°C. Typical examples include lauric acid, myristic acid, palmitic acid, and stearic acid. Fatty acids with a melting point of 50-90°C are preferred. The acids can be employed as the free acids or as their metal salts. Of the possible salts we prefer to use an alkaline earth metal salt of stearic acid. Magnesium and calcium stearates are particularly preferred since they are available in fine particle form.

The wax, fatty acid and/or metal salt thereof are present in the dispersion as fine particles. Appropriate sizes can be determined by trial, but by way of illustration we prefer to use dispersions wherein the particles have an average size of less than 10 microns, preferably less than 5 microns. The smaller the size the better are the resultant films.

Where a wax is employed, either alone or in combination with a fatty acid and/or a salt

thereof, it is one with a melting point of 40-90°C. Typical examples include carnauba wax, whale wax, beeswax, white beeswax and hydrogenated vegetable oils.

The addition of a surface active agent and/or silicone oil to the composition can lower the moisture permeability of the coating film and help to modify the dissolution characteristics. A lowering in moisture permeability cannot be achieved by the simple blending of a surface active agent or silicone oil with a high molecular weight, film-forming, coating polymer, but can be achieved by the use of the fatty acid, the metal salt of a fatty acid, and/or the wax together with a surface active agent. Moreover, the inclusion of a surface active agent in compositions embodying the present invention can improve the lustre and taste characteristics of the resultant product.

Any non-ionic surface active agent may be employed provided it has an HLB of less than 9. Preferred non-ionic surface active agents are the fatty acid esters of sorbitan, with the most preferred examples of surface active agents being sorbitan trioleate and sorbitan monolaurate.

In the formulation of coating compositions which embody the present invention it is feasible to use combinations of two or more of each of the various components. Moreover, use can be made of combinations of the metal salt of a fatty acid, the fatty acid and the wax.

By way of example, preferred coating compositions comprise the following combinations:

(a) white beeswax in an aqueous solution of hydroxypropyl methylcellulose and sorbitan trioleate;

(b) carnauba wax in an aqueous solution of hydroxypropyl methylcellulose and sorbitan trioleate;

(c) white beeswax in an aqueous solution of hydroxypropyl methylcellulose and silicone oil.

If desired, further components may be incorporated in the coating compositions. Food pigments, colouring agents such as titanium oxide, plasticizers such as polyethylene glycol, or perfumes may be added. In order to inhibit bacteria a preservative may be added, e.g. a mixture of methyl, propyl, butyl and ethyl esters of para-hydroxybenzoic acid such as is available under the Trade Mark Parabens.

Coating compositions which embody the present invention can be prepared by dispersing with a suitable dispersing device the wax, the fatty acid and/or the metal salt of a fatty acid in an aqueous solution of the film-forming polymer. The surface active agent and/or silicone oil is usually mixed with the solution of the polymer prior to the formation of the dispersion. Where a metal salt of a fatty acid is employed, this should be added as fine particles. The wax and the higher fatty acid do not have to be added as fine particles, and can be poured as a molten mass into the dispersing device. Certain film-forming polymers will form a gel on heating, but such gelation does not interfere with the formation of the dispersion.

The coating compositions which embody the invention can be stored in a dry form. To this end the invention also provides a solid product obtained by drying a coating composition of the invention. Such solid products can readily be dispersed in water without the need for heating, and used in the same manner as coating compositions which have not been subjected to the drying treatment. We have observed no difference in the moisture permeability of resultant films formed from coating compositions which have and have not been subjected to spray-drying.

The concentration of the solid materials in the coating compositions is not particularly critical, and appropriate values may be obtained by experimentation. When the coating rate of solid material per unit surface area is small, the resultant coating film is susceptible to peeling. On the other hand, when the concentration in the coating solution is too high, a uniform film is not obtained and the product has a rugged surface.

Coating compositions embodying the invention are often easier to coat than an aqueous solution of the same film-forming polymer alone. Thus, for example, aqueous solutions of polymers such as HPMC or HPC are difficult to work with since mutual cohesion between the preparations occurs together with adhesion of the preparations onto the wall of the coating pan or other coating apparatus. We have not observed such adhesion or cohesion when using coating compositions of the present invention and have easily obtained satisfactory films.

The mixing ratios of the wax, the fatty acid and/or the metal salt of a fatty acid can also be determined by experimentation, bearing in mind the desired properties of the coated preparation. Too small an amount of the wax, fatty acid and/or metal salt of the fatty acid leads to a deleterious effect on the lustre and taste, while too much reduces the film-forming ability of the composition and promotes the occurrence of wrinkles and seams. Excess amount of surface active agents should be avoided since this sometimes decreases the moisture permeability of the resultant films. Excess silicone oil should be avoided because it sometimes lowers the adhesive power of the film to the solid preparation.

By way of illustration, we have found that acceptable films can be prepared by using the components in the following amounts (in parts by weight); film-forming polymer up to 30, dispersed fine particles up to 15, surface active agents up to 5, silicone oil up to 5, and water as required to total 100.

The ingestible solid preparations which may be coated using the coating compositions of the present invention include solid pharmaceutical preparations such as tablets, pills and granules. The solid pharmaceutical preparations will typically contain an active ingredient and be in dosage form. However it is to be understood that the present invention is not limited to these particular solid preparations, and, for example, may be used for coating solid food products.

The following Examples are given to illustrate the present invention. Some Comparative Examples are also given. All percentages and parts are by weight.

In certain of the Tables hereinbelow, use is made of the following symbols in the assessments of the characteristic properties of tablets:

X : bad Δ : poor ○ : good

The "masking effect" was assessed from the degree of bitterness with astringency of the active ingredient after a tablet had been rolled on the tongue for 1 minute.

The dissolution test was performed in accordance with the U.S. Pharmacopoeia method, tl indicating the delay in dissolution and t_{50} the time required for dissolution of half the active ingredient. Moisture permeability was assessed by the JIS cup method (Z -0208-1973), 40°C x 90% RH, using films of 100μ thickness.

Examples 1A, 1B, and Comparative Examples 1A, 1B

Four batches of 11kg of tablets, each tablet having ϕ = 6.5 mm, R = 8.0mm, a weight of 100 mg, and containing 50mg of 2-(2-isopropylindan-5-yl)propionic acid, were separately spray-coated with one of the solutions A to D shown in Table 1. The properties of the thus coated tablets and of the uncoated tablets are shown in Table 2.

Table 1

	Coating Composition (%)			
	Comparative Example 1A "CE 1A"	Comparative Example 1B "CE 1B"	Example 1A "E 1A"	Example 1E "E 1B"
HPMC	10	10	10	10
White beeswax	0	2	2	2
Sorbitan trioleate	0	0	0.2	0.2
Water	90	88	87.8	10
Ethanol	0	0	0	77.8

Table 2 Results of Tests

	Uncoated Tablets	Coated Tablets							
		CE1A		CE1B		E1A		E1B	
Amount of solid material coated (mg/T)	0	3.6	4.8	3.6	4.8	3.6	4.8	3.6	4.8
Lustre	X	X	X	○	○	○	○	○	○
Taste	X	X	X	○	○	○	○	○	○
Masking effect	X	X	Δ	Δ	○	○	○	○	○
Dissolution (min) tl	0.1	0.6	1.0	0.8	1.1	1.3	3.5	1.5	4.1
t_{50}-tl	1.1	1.0	1.3	1.2	1.2	1.1	1.1	1.1	1.1

Example 2

In a coating vessel was placed 11 kg of tablets, each with ϕ = 8.5 mm, R = 10.5mm, a weight of 220mg and containing 50mg of 2-(2-isopropylindan-5-yl)propionic acid. The tablets were spray-coated with the coating composition shown in Table 3 until the solid

coating film amounted to 4mg/T.

Table 3 Coating Composition (%)

HPMC	5
White beeswax	1
Sorbitan trioleate	0.1
Water	93.9

The tablets coated with the above composition had a good lustre and smooth taste, and the characteristic bitterness with astringency of the active ingredient could not be perceived after rolling a tablet on the tongue for 1 minute. The dissolution test was also carried out with the uncoated tablet for comparison and the results obtained plotted as release curves. These release curves are shown in the Figure, wherein curve 1 is the release curve of the tablet coated with the composition of Table 3 and curve 2 is the curve of the uncoated tablet. A definite delay in dissolution is clearly seen for the tablet coated with the above composition, and the subsequent dissolution pattern is about the same as that of the uncoated tablet. This plot thus indicates that the coating does not affect the release rate, but merely delays the onset of release.

Example 3

Three 11 kg batches of tablets were placed in turn in a coating vessel, each tablet having ϕ = 8.5mm R = 10.5mm, a weight of 220 mg and containing 3mg of sodium benzoate. The batches were spray-coated until the solid coating film amounted to 5.3mg/T with one of the compositions shown in Table 4. The results of testing the three batches of coated tablets are shown in Table 5, together with the results for uncoated tablets.

Table 4 Coating Composition (%)

	A	B	C
HPMC	12.5	12.5	12.5
White beeswax	2.5	0	0
Carnauba wax	0	2.5	0
Stearic acid	0	0	2.5
Silicone oil KS 66*	0.25	0.25	0.25
Water	84.75	84.75	84.75

* Available from Shin-Etsu Chemical Co., Ltd.

Table 5 Results of Tests

	Uncoated tablets	Coated Tablets		
		A	B	C
Effectiveness of coating film formation	-	○	○	○
Lustre	X	○	○	○
Taste	X	○	○	○
Dissolution (min) t1	0.1	1.3	1.4	1.4
Dissolution (min) t_{50}-t1	0.4	0.4	0.4	0.4

Example 4 and Comparative Example 2

Two 2 kg batches of tablets each having Ø = 8.5mm, R = 10.5mm, a weight of 220 mg and containing 50mg of 2-(2-isopropylindan-5-yl)propionic acid were spray-coated in a coating vessel with one of the compositions shown in Table 6 until the solid material coating film amounted to 4.3mg/T. The compositions were prepared by first dissolving the HPMCP in aqueous 0.1N-NaOH solution, then the wax and sorbitan trioleate were added and the mixture thus obtained dispersed with a Homomixer while heating.

The results of the tests with the coated and uncoated tablets are shown in Table 7.

Table 6 Coating Composition (%)

	Comparative Example 2	Example 4
HPMCP	10.0	10.0
NaOH	1.0	1.0
White beeswax	0	2.0
Sorbitan trioleate	0	0.2
Water	89.0	86.8

Table 7 Results of Tests

		Coated Tablets: Comparative Example 2	Coated Tablets: coated Example 4	Uncoated tablets
Ability of coating film formation		○	○	-
Lustre		△	○	X
Taste		△	○	X
Dissolution (min)	tl	1.5	3.0	0.2
	t_{50}-tl	1.5	1.5	1.6

Example 5 and Comparative Example 3

In a coating vessel was placed 1 kg of tablets each with ϕ = 8.5mm, R = 10.5mm, a weight of 220 mg and containing 10mg of sodium benzoate. They were then spray-coated with one of the compositions in Table 8 until the solid coating film amounted to 4.3mg/T. The coating compositions were prepared by dissolving the AEA and fumaric acid in water and adding the wax and sorbitan trioleate. The mixture thus obtained was dispersed while heating with Homomixer.

The results of the tests with the coated and uncoated tablets are shown in Table 9.

Table 8 Coating Composition (%)

	Comparative Example 3	Example 5
AEA	10.0	10.0
Fumaric acid	0.9	0.9
White beeswax	0	2.0
Sorbitan troleate	0	0.2
Water	89.1	86.9

Table 9 Results of Tests

		Coated Tablets: Comparative Example 3	Coated Tablets: Example 5	Uncoated tablets
Effectiveness of coating film formation		○	○	-
Lustre		△	○	X
Taste		X	○	X
Dissolution (min)	tl	1.0	2.5	0.1
	t_{50}-tl	1.2	1.2	1.1

Example 6

To a solution prepared by dissolving 12.5 parts of HPMC in 84.75 parts of water were added 2.5 parts of beeswax and 0.25 parts of sorbitan trioleate. The mixture was warmed to the fusion point of beeswax, and then dispersed with a Homomixer. After cooling to below 40°C while continuing the dispersing operation, the liquid thus dispersed was diluted threefold with water, and subsequently spray-dried with an "Anhydro Spray Dryer" (made in Denmark) using drying air at 100-110°C and a spray disk operated at 45,000 rpm. The particle size of the spray-dried powder was about 100 μ. A coating composition was prepared from the dried powder with a stirrer, and the particle size of the beeswax was of the same order as in the dispersion before spray-drying. Test films were then prepared, either with the coating composition thus prepared, or with the dispersion obtained prior to spray-drying. No difference before and after spray-drying was observed in the moisture permeability, which was 261 [$H_2O.g/m^2/day$], nor in any of the other characteristics of the coating films. Tablets were coated in the manner of the previous Examples and gave an acceptable product.

Examples 7 to 10 and Comparative Examples 4 to 9

Coating films were prepared using the coating compositions shown in Tables 10 and 11. An important ability of the present compositions is to form a protective, moisture proof film, and this effect is shown in Table 10 using various coating compositions. The effect of using a surface active agent together with a wax is shown in Table 11. Tablets were coated using each of the listed compositions embodying the invention and found to have acceptable films.

In the column headings of the tables 10 and 11, the abbreviations 'E' and 'CE' respectively stand for 'Example' and 'Comparative Example'.

Table 10 Effect of Various Coating Compositions [%]

	CE4	CE5	CE6	CE7	CE8	E7	E8	E9
HPMC	100	83.3	83.3	98.0	83.3	82.0	82.0	82.0
Beeswax	-	16.7	-	-	8.35	16.4		16.4
Stearic acid	-	-	16.7	-	8.35	-	16.4	-
Sorbitan trioleate	-	-	-	2.0	-	1.6	1.6	-
Silicon oil KS-66	-	-	-	-	-	-	-	1.6
Solvent employed	water	water	water	water	water	water	water	water
Moisture permeability [$H_2O.g/m^2/day$]	550	355	354	693	391	251	245	301

Table 11

Effect of Addition of Surface Active Agent [%]

	CE9	E10
HPMC	83.3	82.0
Beeswax	16.7	16.4
Sorbitan trioleate	-	1.6
Solvent employed	water	water
Moisture permeability [$H_2O.g/m^2/day$]	355	251

As can be clearly seen from Table 10, the coating film formed from the compositions embodying the invention exhibited superior moisture proof properties as compared with those of the controls using HPMC without the surface active agent or silicone oil. The beneficial results of using the surface active agents in combination with beeswax and/or stearic acid can be seen in Tables 10 and 11. As shown in Table 10, a control coating film composed of the water-soluble high molecular weight film-forming compound and the

surface active agent did not provide any improvement as compared with that of the water-soluble high molecular weight compound alone. To the contrary, addition of the surface active agent alone deteriorates the quality of the coating film.

WHAT WE CLAIM IS:-

1. An ingestible coating composition which comprises a non-toxic dispersion of particles dispersed in an aqueous solution of a film-forming polymer, the particles comprising one or more of a metal salt of a fatty acid which acid has a melting point of 40-90°C, a fatty acid having a melting point of 40-90°C, or a wax having a melting point of 40-90°C, and the aqueous solution further containing a non-ionic surface active agent with an HLB of less than 9 and/or a silicone oil.

2. A coating composition according to Claim 1 wherein the film-forming polymer is hydroxypropyl cellulose, hydroxypropyl methylcellulose, a salt of polyvinyl acetal diethylaminoacetate, a salt of cellulose acetate phthalate, a salt of hydroxypropyl methylcellulose phthalate, methylcellulose, hydroxyethylcellulose, sodium carboxymethylcellulose, polyvinyl alcohol, polyvinylpyrrolidone, sodium alginate or a salt of an acrylate polymer.

3. A coating composition according to Claim 2 wherein the film-forming polymer is hydroxypropyl cellulose, hydroxypropyl methylcellulose, a salt of polyvinyl acetal diethylaminoacetate or a salt of hydroxypropyl methylcellulose phthalate.

4. A coating composition according to Claim 3 wherein the salt of polyvinyl acetal diethylaminoacetate is a salt with a dibasic organic carboxylic acid.

5. A coating composition according to Claim 3 wherein the salt of hydroxypropyl methylcellulose phthalate is an alkali metal or ammonium salt.

6. A coating composition according to Claim 2 wherein the salt of cellulose acetate phthalate or of an acrylate polymer is an alkali metal or ammonium salt.

7. A coating composition according to any one preceding Claim wherein the metal salt of a fatty acid is an alkaline earth metal salt of stearic acid.

8. A coating composition according to Claim 7 wherein the metal salt is magnesium or calcium stearate.

9. A coating composition according to any one preceding Claim which contains said fatty acid, wherein the said fatty acid is lauric acid, myristic acid, palmitic acid or stearic acid.

10. A coating composition according to any one preceding Claim which contains said wax, wherein the wax is carnauba wax, whale wax, beeswax, white beeswax or a hydrogenated vegetable oil.

11. A coating composition according to any one preceding Claim wherein the surface active agent is a fatty acid ester of sorbitan.

12. A coating composition according to claim 11, wherein the surface active agent is sorbitan trioleate or sorbitan monolaurate.

13. A coating composition comprising a dispersion of particles of white beeswax dispersed in an aqueous solution of hydroxypropyl methylcellulose and sorbitan trioleate.

14. A coating composition which comprises a dispersion of particles of carnauba wax dispersed in an aqueous solution of hydroxypropyl methylcellulose and sorbitan trioleate.

15. A coating composition which comprises a dispersion of particles of white beeswax dispersed in an aqueous solution of hydroxypropyl methylcellulose and silicone oil.

16. An ingestible coating composition substantially as hereinbefore described in any one of the Examples.

17. A solid product obtained by drying a coating composition according to any one preceding Claim.

18. A solid product according to Claim 17 when obtained by spray-drying the coating composition.

19. A coating composition obtained by addition of water to a solid product according to Claim 17 or Claim 18.

20. A method of forming a protective film on an ingestible solid preparation which comprises coating the preparation with a coating composition according to any one of Claims 1 to 16 or 19, and causing or allowing water to evaporate from the coating.

21. An ingestible solid preparation when coated with a protective film by a method according to Claim 20.

22. A solid preparation according to Claim 21 which is a pharmaceutical preparation.

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